REMARKS

Claims 1-11, 13, 14, 16-74, 76-83, 87-132, 134, 135, 138 and 142 are pending. Claim 1 was amended and claim 88 was cancelled. Support for the amendment to claim 1 can be provided through the specification. Claims 1-11, 13, 16-43, 72-74, 87-97, 134 and 135 have been rejected. Claims 44-71, 76-82 and 92-132 have been withdrawn, and Claims 12, 15, 75, 84-86, 133, 136, 139-141 and 143 have been canceled without prejudice. Applicants reserve the right to pursue withdrawn and canceled claims in a divisional or continuing application.

Reconsideration and withdrawal of the pending rejections in view of the below remarks are respectfully requested.

Applicants wish to thank the Examiner for taking the time to review and consider previously proposed arguments, and proceeding with withdrawing the Enablement rejection in favor of the 103 rejections, as well as withdrawing the Written Description rejection in favor of the 103 rejections claim amendments with respect to Claims 1-43, 72-75, 83-91, 133-143 and the 103 rejections thereto.

Applicants note the omission of C56, C75, C248, and C293 are missing. These references are being submitted with this Response and Applicants respectfully request their consideration.

A. Response to Rejections under 35 U.S.C. § 112, first paragraph

1. Written Description

Claims 1, 4, 16-18, and 25 have been newly rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the Specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Claim 25 allegedly lacks written description because claim 25 is drawn to a CMV promoter and a beta-actin promoter in combination.

The standard for the written description requirement has already been discussed in the prosecution of this application (See for example, Response to Office Action dated Dec 7, 2004).

The Examiner asserts that the "specification and art provide adequate written description for a CMV promoter and a beta-actin promoter . . . [but the they do not provide] guidance to arrive at [a] one that is a combination of the two. The Examiner is respectfully directed to the

specification which provides for a chicken beta-actin/CMV fusion promoter and cites Daly et al. Gene Ther 8: 1291-8 (2001). Daly et al. was cited and provided as A45 in the PTO 1449 submitted on March 7, 2005. In addition, references are provided as evidence showing use of combination promoters as promoters was successfully achieved. Beattie SG, et al., "Recombinant adeno-associated virus-mediated gene delivery of long chain acyl coenzyme A dehydrogenase (LCAD) into LCAD-deficient mice," J Gene Med. 2008 Aug 21; Klein RL, et al., "AAV8, 9, Rh10, Rh43 vector gene transfer in the rat brain: effects of serotype, promoter and purification method," Mol Ther. 2008 Jan;16(1):89-96. Epub 2007 Oct 23; Song S, et al., "Stable therapeutic serum levels of human alpha-1 antitrypsin (AAT) after portal vein injection of recombinant adeno-associated virus (rAAV) vectors," Gene Ther. 2001 Sep;8(17):1299-306; Nguyen AT, et al., "Evaluation of gene promoters for liver expression by hydrodynamic gene transfer," J Surg Res. 2008 Jul;148(1):60-6. Epub 2008 Mar 13; Tenenbaum L, et al., "Recombinant AAV-mediated gene delivery to the central nervous system," J Gene Med. 2004 Feb;6 Suppl 1:S212-22.

The specification does provide written description for CMV promoters, beta-actin promoters, and combination promoters. In addition, those of skill in the art, at the time of the filing of the patent application, understood how to use promoters in conjunction with other promoters to give desired properties over the use of either promoter alone, as evidenced by publications showing successful use.

This rejection is respectfully traversed and withdrawal is requested.

2. Enablement

Claims 1, 4, 6, 16-18, 25, 26, 29, 30, and 87-89 were rejected under 35 U.S.C. § 112, first paragraph, because the specification allegedly lacks enablement as claim 25 is drawn to a combination promoter of beta-actin and CMV. The Examiner maintains this rejection because allegedly "neither the art nor the specification provides any guidance as to what steps would be required such that an artisan, would arrive at this hybrid promoter." As discussed above, the specification does provide examples of combination promoters, such as the chicken beta-actin/CMV fusion promoter.

The Examiner has also argued that claims drawn to a HEXB product do not meet the limitation of catabolizing GM_2. Applicants point out that the claims do meet the limitation of catabilozing GM_2. As pointed out at paragraph 62 of the specification,

> The catabolism of the GM_2 ganglioside in mammalian cells is mediated by β-hexosaminidase, a lysosomal acidic hydrolase. The lysosomal enzyme β-hexosaminidase (HEX) is comprised of 2 subunits (peptides), HEX-α and HEX-β, encoded by two distinct genes, HexA and HexB, respectively. β-hexosaminidase exists in 3 isoforms (proteins), HEXA (α/β heterodimer), HEXB (β/β homodimer) and HEXS (α/α homodimer). HEXA is rate limiting in GM_2 catabolism in humans.

Note that the limitation at issue, "wherein the HEX-β and HEX-α can form a dimer, and wherein the dimer can catabolizeGM2 ganglioside *in vivo*" makes clear that the activity being discussed is activity by the dimer, which must be a HEXA, not a HEXB dimer, as the dimer of the phrase is made of HEX-β and HEX-α. Thus, the Examiner's concerns regarding the lack of a functional GM_2 activity from a HEXB dimer is moot. This rejection is respectfully traversed.

Claim 88 has been cancelled without prejudice to facilitate prosecution, and so the issues regarding the sequence of SEQ ID NO:69 and the NSE promoter are moot.

This rejection is respectfully traversed and withdrawal is requested.

B. Response to Rejections under 35 U.S.C. § 112, second paragraph

Claim 22 was rejected under 35 U.S.C. § 112, second paragraph because claim 22 is drawn to a mammalian sequence, which depends from an Avian sequence (claim 21). Claim 22, has been amended to depend from claim 20, as it was inadvertently depended from claim 21. Applicants point out, however, that this amendment is made merely to facilitate prosecution as a skilled artisan would know how to use hybrid promoters, as is discussed above with the hybrid CMV/beta-actin promoters.

C. Response to Rejections under 35 U.S.C. § 103

Claims 1-11, 13, 16-21, 23, 24, 26-28, 31-39, 43, 72-74, 134, and 135 were rejected under 35 U.S.C. § 103 as allegedly obvious over Brown and Mahuran, 1993, American Journal of Human Genetics, 53:497-508, in view of Li and Li, 2001 International Congress Series, 1223: 3-15, Rossi et al., 1998, Nature Genetics, 20: 389-393, Kim et al., 1992, Molecular and Cellular Biology, 12: 3636-3643, Proia, 1988, PNAS, USA, 85: 1883-1887, Myerowitz et al., 1985,

PNAS, USA, 82: 7830-7834, Patapoutian et al., WO 02/101045 A2, published December 19, 2002, Hobbs [online], 1997 [retrieved on 2008-03-02]. Retrieved from the Internet:< URL: http://www.ncbi.nlm.nih.gov/entrez/viewer.fcgi?cmd=Retrieve&db=Nucleotide&list uids=2329859&dopt=GenBank&WebEnv=Onpmz046m-ZDooSIRzuukhPw99ul5bvKx98CayPd0_uLYe5w4_-6eC9cd-KucPViMuvowjZ0gwTJT%40256362576FC165A0_0107SID&WebEnvRq=1>, pages 1-3, Hennighausen and Fleckenstein, 1986, EMBO Journal, 5: 1367-1371, Kost et al., 1983, Nucleic Acids Research, 11: 8287-8301, Kistner et al., 1996, PNAS, USA, 93: 10933-10938, Sauer, 1998, Methods, 14:381-392, Banerjee et al., 1994, The Journal of Biological Chemistry, 269: 4819-4826.

1. Law

The Patent & Trademark Office (PTO) carries the burden of first showing that a *prima facie* case of obviousness exists, upon which time the burden shifts to the Applicant to rebut this *prima facie* case. Teaching away is one form of rebuttal.

The U.S. Patent and Trademark Office has the burden under 35 U.S.C. § 103 to establish a *prima facie* case of obviousness. *In re Warner et al.*, 379 F.2d 1011, 154 U.S.P.Q. 173, 177 (C.C.P.A. 1967), *In re Fine,* 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598-99 (Fed. Cir. 1988). In rejecting a claim under 35 U.S.C. § 103, the Examiner must establish a *prima facie* case. Under §103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or non-obviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented." *Graham* v. *John Deere Co. of Kansas City*, 383 U. S. 1 (1966) *Id.*, at 17-18.

A single line in a prior art reference should not be taken out of context and relied upon with the benefit of hindsight to show obviousness. Bausch & Lomb, Inc. v. Barnes-Hind/Hydracurve, Inc., 796 F.2d 443, 230 U.S.P.Q. 416 (Fed. Cir. 1986), cert. denied, 480 U.S. 823 (1987). Claims are not to be read in a vacuum, and limitations therein are to be interpreted in light of the specification in giving them their broadest reasonable interpretation. In re Marosi

710 F.2d 799, 218 U.S.P.Q. 289 (Fed. Cir. 1983) "Claims must be read in view of the specification, of which they are a part." Markman, 52 F.3d at 979 (citing Autogiro Co. of Am. v. United States, 384 F.2d 391, 397, 155 U.S.P.Q. 697, 702 (Ct. Cl. 1967)).

"Focusing on the obviousness of substitutions and differences, instead of on the invention as a whole, is a legally improper way to simplify the often difficult determination of obviousness." Gillette Co. v. S.C. Johnson & Sons, Inc., 919 F.2d 720, 724, 16 U.S.P.Q.2d 1923 (Fed. Cir. 1990); Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1383, 231 U.S.P.Q. 81, 93 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987). "One cannot use hindsight reconstruction to pick and choose among isolated disclosures on the prior art to deprecate the claimed invention." In re Fine, 837 F.2d 1071, 1075 (Fed. Cir. 1988).

Claims for an invention are not *prima facie* obvious if the primary references do not suggest all elements of the claimed invention and the prior art does not suggest the modifications that would bring the primary references into conformity with the application claims. *In re Fritch*, 23 U.S.P.Q.2d, 1780 (Fed. Cir. 1992). *In re Laskowski*, 871 F.2d 115 (Fed. Cir. 1989). This is not possible when the claimed invention achieves more than what any or all of the prior art references allegedly suggest, expressly or by reasonable implication.

A situation where it would be obvious to try or test is a particular construct or method is insufficient to meet the standard of obviousness. The current rejections are analogous to the rejection deemed improper by the Federal Circuit (In re Deuel, 34 USPQ2d 1210 (Fed. Cir. 1995)). In Deuel, the Court reaffirmed that a rejection based on an "obvious to try" standard was improper. The Court specifically found that prior art that teaches a method for obtaining a general result, when the actual results are unknown, is insufficient to make obvious the actual results obtained upon which the claims are based. In pertinent part, the Deuel Court states

> "A general motivation to search for some gene that exists does not necessarily make obvious a specifically-defined gene that is subsequently obtained as a result of that search."
>
> "Thus, even if, as the examiner stated, the existence of general cloning techniques, coupled with knowledge of a protein's structure, might have provided motivation to prepare a cDNA or made it obvious to prepare a cDNA, that does not necessarily make obvious a particular claimed cDNA. 'Obvious to try' has long been held not to constitute obviousness". Id.

Thus, in Deuel, the Federal Circuit clearly sets forth a limitation on making a *prima facie* case of obviousness, this limitation being "obvious to try."

Furthermore, it is axiomatic that evidence which teaches away from the claimed compositions or molecules provides significant evidence of non-obviousness. *In re Hedges*, 228 USPQ at 687.

2. Analysis

As discussed below, the present rejection fails to make a prima facie case of obviousness, as there is no suggestion or motivation to arrive at the claimed constructs, there is not a reasonable expectation of success using the claimed constructs, at best the art presented in the rejection makes it obvious to try, and lastly there is a significant teaching away from the claimed constructs.

i. Brown and Mahuran ("Brown")

Brown and Mahuran disclose transfection of a mutant *HEX*A gene producing a mutant α-subunit producing mutant HexA activity in Cos cells. Brown does not disclose expression of *HEX*A and *HEX*B on a single plasmid to produce a functional Hex-A product *in vivo*.

With respect to obviousness this is very important because the Cos cell system used by Brown does not have native Hex-α, nor mutant Hex-α for that matter, as is the case *in vivo*. Being able to show the production of Hex-α in a system in which there is no competing Hex-α to disrupt the transfected produced *Hex*A or *Hex*B. In fact, this turns out to be very important, as has been discussed earlier in the prosecution of this application, initial attempts at in vivo substitution of Hex-α in the presence of endogenous Hex-α, particularly mutated, is very difficult to achieve, and in fact, teaches away from a bicistronic vector, producing both *Hex*A and *Hex*B, actually working.

D. Claims 1-11, 13, 16-21, 23, 24, 26-28, 31-39, 43, 72-74, 134, and 135 are not obvious

1. No suggestion or motivation present or provided

i. Mere presentation of sequence is insufficient to make a combination of sequences obvious

The Office Action cites Brown, Li and Li, Rossi et al., Kim et al., Proia, Myerowitz et al., Patapoultan et al., WO 02/101045 A2, Hobbs, Hennighausen and Fleckenstein, Kost et al., Kistner et al., Sauer, and Banerjee et al. as allegedly providing one or more pieces of the

complete nucleic acids present in one or more of claims 1-11, 13, 16-21, 23, 24, 26-28, 31-39, 43, 72-74, 134, and 135.

The rejection relies on Brown and Mahuran for

> clones of human HEXA and human HEXB with a substitution, cloned into various vectors, cotransfection into COS cells, obtaining reduced function HexA, SV40 promoter, artificial substrate of GM2 catabolism (Brown fails to provide an IRES, single plasmid system)

Kim et al., for

> an IRES sequence, (although no connection between Kim et al. and Brown at all)

The Examiner asserts it would have been obvious to combine the information of Brown with the IRES sequence of Kim et al. to arrive at the claimed constructs. This fails because there is no suggestion or motivation provided by these references, or other references, to arrive at the claimed nucleic acids, there is no expectation of success with the claimed compositions, the combination provided by the rejection amounts to merely an obvious to try standard for the combination and the result, and significantly, there is a significant teaching away from the very combination the rejection tries to make.

Alone or in combination, these references fail to even make a *prima facie* case of obviousness. For the sake of brevity, Applicants are not currently arguing whether the references actually teach the specific sequences recited in the specification as their combination fails, even if the sequences are correct. However, Applicants reserve the right to argue this, should it be found that a *prima facie* case of obviousness is established by the mere referral to references containing alleged subparts of a claimed nucleic acid.

ii. No motivation suggestion to combine in Brown and Mahuran or Kim et al.

Neither Kim et al. nor Brown provide a motivation to combine HEX-α and HEX-β into a single vector with an IRES sequence such that these vectors can be expressed in the brain.

Brown at least, does not teach the following which would at least be necessary to make claims 1-11, 13, 16-21, 23, 24, 26-28, 31-39, 43, 72-74, 134, and 135 obvious and there is not motivation or suggestion to combine any other reference to alleviate these deficiencies. Brown does not teach the expression or production of both HEX-α and HEX-β from a bicistronic gene.

This, at least, would be required to make claims 1-41, 72-75, 83-91 obvious. Moreover, Brown does not teach the construction of lentiviral bicistronic vectors. In addition, Brown does not teach the expression of any set of two genes by an IRES-barring bicistronic vector in whole animals *in vivo*. Brown does not teach about the order of the bicistronic gene comprised of *HEX*A and *HEX*B.

Kim et al., at least, do not teach the following which would at least be necessary to make claims 1-11, 13, 16-21, 23, 24, 26-28, 31-39, 43, 72-74, 134, and 135 obvious and there is not a motivation or suggestion to combine any other reference to alleviate these deficiencies. Kim et al. does not teach anything about HEX-α and HEX-β. Kim et al. does not teach anything about the use of the lentiviral vector to transduce brain cells. Kim et al. does not teach anything about the treatment or amelioration of Tay Sachs or Sandoff's diseases, for example. Kim et al. does not teach anything about the order of the bicistronic gene comprised of HEX-β and HEX-α.

Applicants understand the Office Action's combination rejection to be summarized as follows: 1) the individual pieces of the claimed nucleic acids were known (p. 8 and 9 of the Office Action) (except for the FIV vector, in this rejection), 2) Brown showed that two (non FIV) vectors could infect COS cells (p. 8, of the Office Action), and 3) Kim et al. allegedly teach the expression of two proteins from a bicistronic gene using an IRES sequence (p. 9, of the Office Action) with the conclusion being,

> "It would have been obvious to one of ordinary skill in the art to take Kim et al's teaching of using an IRES in an expression vector such that [Hex A] *Hex*A and [Hex B] *Hex*B can be expressed from one vector. (p. 9, of the Office Action).

The Examiner has attempted to combine 14 references to arrive at the present rejections, and has not pointed to a single spot in any of the references where there was even a hint, much less a suggestion or motivation, to arrive at the claimed nucleic acids. The mere assertion that the skilled artisan would have found it obvious is insufficient to meet a case for *prima facie* obviousness. No argument, much less evidence, that the skilled artisan would conclude so is provided. More is needed when only two references are combined, and much more is needed when 14 references are combined. Surely when a combination of 14 references is used, there must be, at least a suggestion to combine any two of the 14 references, and even this is lacking in the references and thus cannot be present in the rejection.

2. Reasonable Expectation of Success

The Examiner has provided no evidence that a reasonable expectation of success that the claimed compositions, all of which are based on HEX-β and HEX-α, being expressed from a single vector, such that they would produce β-hexosamindase, would work. The Examiner has not even asserted the same. Production from two vectors to produce a functional Hex-α is not the same as production from a single vector, whether an IRES sequence was known or not. There is no indication that the correct stoichiometry would be present from a single vector, and more importantly there is not indication that the correct stoichiometry could be achieved in vivo. Note that the claims as amended are drawn to having function *in vivo*.

3. Secondary considerations

It is clear, that even if a *prima facie* case of obviousness is made, which Applicants dispute here, the *prima facie* case of obviousness can be rebutted by what have been called secondary factors. One of the secondary factors that makes something non-obvious is a teaching away from the claimed invention. In this case, there is just such a teaching. Previous attempts to provide *HEX*A and *HEX*B. in vivo, *on separate plasmids, much less a single plasmid*, were unsuccessful. Thus, the starting point for the skilled artisan was that nucleic acids and vectors sufficient for gene therapy related to HEX-β and HEX-α. did *not* work. How can the skilled artisan have had a reasonable expectation that the claimed nucleic acids would work in this environment?

A simple substitution of the reporter gene lacZ by *HEX*A or *HEX*B would not have been efficacious in restoring the activity of a functional β-hexosaminidase enzyme (α/β hetero-dimmer) as taught by the work of Guidotti et al. (Guidotti JE, Mignon A, Haase G, et al. Adenoviral gene therapy of the Tay-Sachs disease in hexosaminidase A-deficient knock-out mice. Hum Mol Gen 8, 831-838, 1999). Specifically, Guidotti et al. demonstrated that administration of viral vectors (adenoviral gene therapy) encoding for HEX-α or HEX-β alone **were not** sufficient in restoring β-hexosaminidase activity *in vivo*. Furthermore, simultaneous administration of such adenoviral vectors resulted in a very high Hex-A activity in the liver (9-fold more than the normal value) and in partial or total correction in other tissues: 95% of the normal activity in the heart, 51% in skeletal muscle, 40% in spleen and 34% in kidney. Furthermore, Guidotti et al. did not see activity in the brain. Guidotti et al. shows that, "the

activity in the brain was not significantly increased". (p. 832, col 2, ll. 18-19). In contrast the *in vivo* date provided in the present specification shows that the claimed bicistronic vectors do provide significant expression in the brain.

Not only must the HEX-α and HEX-β subunits be expressed, the HEX-α and HEX-β subunits must properly and stoichiometrically associate and come to the formation of a single functional β-hexosaminidase enzyme (α/β hetero-dimmer): HEX-α peptide must associate with one HEX-β peptide. However, two HEX-α peptides can associate to form the protein HEX-S, as well as two HEX-β peptides can associate to form the protein HEX-B. However, only the association of one HEX- α and one HEX- β peptide results in the formation of a functional β-hexosaminidase enzyme capable of metabolizing the GM2 ganglioside, storage of which results in the development of Tay-Sachs or Sandhoff disease. Moreover, the HEX-β peptide has higher affinity for it self than HEX-α for it self, resulting in a competition between the HEX-α and HEX-β subunits in the formation of the various isoforms of β-hexosaminidase (HEX-A, HEX-B and HEX-S). Subsequently, HEX-β must exist in over-abundance in the micro-environment for HEX-β to associate with HEX-α in the formation of a functional β-hexosaminidase enzyme (α/β hetero-dimmer).

There is nothing that would lead one to the claimed nucleic acids to have this type of result, and there is nothing that would provide a reasonable expectation of success that the claimed nucleic acids would function. In fact, it is just the opposite, as taught by Guidotti et al., one did not even think they could be *expressed* appropriately in the brain. Applicant therefore respectfully requests the withdrawal of this rejection.

4. Supporting references

The rejection relies on Prioa and Myerowitz et al., to supply variant HexA and HexB sequences, and Patapoutian et al., for teaching conservative changes and for asserting conservative changes would have been obvious, as to claim 1 and 72. The rejection relies on Kim et al, for the orientation of the HexA and HexB around the IRES sequence, being "a matter of design" for claims 2, 5, and 7-9. As discussed above, this orientation can play a crucial role in stoichiometry of production of the Hex-A and the Hex-B. The rejection also relies on Kim et al. for using a second IRES sequence (claims 10, 11) and using a reporter gene (claims 31-32) to make obvious using a second IRES to produce a reporter construct. The rejection relies on

Hobbs for asserting the obviousness of the particular IRES sequence of claim 16. The rejection also relies on the SV40 promoter to make obvious constitutive promoters of claims 17-23, on Henninghausen and Fleckenstein to make obvious the use of the CMV promoter of SEQ ID NO:32, and on Kost et al., to make obvious the beta actin promoter of claim 26. In addition, the rejection relies on Kistner et al., to teach and make obvious inducible promoters of claim 24. The rejection also relies on Sauer to teach and make obvious the recombinase sites (claims 31-34), a termination site flanked by recombinase sites (claims 35-38) (with the assertion that simply following a circular plasmid around will eventually bring you back to the 5' end, having a termination sequence). The rejection relies on Brown to assert that because the COS cells produced HexA and HexB the cells would have made obvious the production of the HexB, HexA, and HexS of claims 26-28. The rejection relies on Banerjee et al. to teach and make obvious expression constructs stably integrated into a genome (claims 39, 43). These rejections are respectfully traversed. As discussed above, it is noted that there has been no attempt to link these references together with the base references in the context of the present claims. Just because the elements are present, a hindsight rejection, asserting that it would have been obvious to combine these elements nor if combined that there would be a reasonable expectation of success. This does not produce a *prima facie* obviousness case. Applicants reserve the right to argue these references if the Examiner does not find the arguments herein regarding the compositions of claim 1 persuasive.

Claims 1, 4, 6, 39-42, 87, 90, and 91 were rejected under 35 U.S.C. § 103 as allegedly obvious over Brown, in view of Li and Li, Kim et al., Chavany and Jendoubi, Schuette et al., Litchtler et al., and Klimatcheva et al.. This rejection relies on the additional teachings to support the deficiencies of Brown, Li and Li, and Kim et al. with regards to neural specific promoters and a lentiviral vector.

The rejection asserts Chavany and Jendoubi teach lipid accumulation from defective GM2 catabolism, and that this occurs in neural centric organs. The rejection asserts that the skilled artisan would want to switch the constitutive promoter with a neural specific promoter, to localize the expression in neural tissue (neural promoter, claim 88). It is asserted that Schuette et al., teach that skin is affected in Tay-Sachs and Sandoff patients making obvious using the skin promoter of claims 90-91.

It is asserted that Chavany and Jendoubi teach that a problem with gene therapy is crossing of the blood brain barrier. The rejection asserts that to overcome this HSV and adenovirus vectors can be used, and that Chavany and Jendoubi teach that HIV can be used to overcome the problems of retroviral vectors infecting latent neural cells. The rejection asserts that Klimatcheva teach the use of an FIV vector and that this would be as likely to use as an HIV vector. Therefore, it is asserted, the claims would have been obvious. As discussed above, it is noted that there has been no attempt to link these references together with the base references in the context of the present claims. Just because the elements are present, a hindsight rejection, asserting that it would have been obvious to combine these elements nor if combined that there would be a reasonable expectation of success. This does not produce a *prima facie* obviousness case. Applicants reserve the right to argue these references if the Examiner does not find the arguments herein regarding the compositions of claim 1 persuasive.

E. Examiner's Note

Applicant's note the Examiner's careful review of the sequences of the application and specifically with respect to SEQ ID NO:1. Note Applicants have edited claim 1 to be based on the opening reading frame of SEQ ID NO:2 which is a correct human HEX-α gene.

Thus, applicants respectfully submit that the invention as recited in the claims as presented herein is allowable over the art of record, and respectfully request that the respective rejections be withdrawn.

CONCLUSION

Based on the foregoing amendments and remarks, Applicants respectfully request reconsideration and withdrawal of the rejection of claims and allowance of this application. Favorable action by the Examiner is earnestly solicited.

No fees are believed to be due; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 50-4667.

Respectfully submitted,

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